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ORIGINAL CONTRIBUTIONS

A Time Interval of More Than 18 Months Between a Pregnancy and a Roux-en-Y Gastric Bypass Increases the Risk of Iron Deficiency and Anaemia in Pregnancy

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Abstract
Objective The aim of the study is to explore the impact of time between Roux-en-Y gastric bypass (RYGB) and pregnancy on obstetrical outcome and nutritional derangements.
Methods In a retrospective cross-sectional study of pregnant women admitted for antenatal care at two tertiary hospitals, we examined 153 women with RYGB and a singleton pregnancy of at least 24 weeks. The women were stratified according to a pregnancy <18 months (40 women) or ≥18 months (113 women) after RYGB. Main outcome measures were nutritional parameters and glycated haemoglobin 1Ac (HbA1c) in second and third trimester of pregnancy, gestational hypertension, length of pregnancy, mode of delivery and foetal birth weight.
Results The two groups were comparable regarding age, parity and prepregnancy body mass index. The frequency of iron deficiency anaemia (ferritin <12 μg/L and haemoglobin <6.5 mmol/L/10.5 g/dL) was significantly higher in the late group, 29 vs. 8 % in the early group, $p = 0.010$. No differences were found for vitamin B_{12}, vitamin D and zinc. Median HbA1c was significantly higher in the late group than in the early group (33 vs. 31 mmol/mol, $p = 0.027$). There were no significant differences in the risk of adverse pregnancy outcome or birth weight between the two groups.
Conclusion A long surgery-to-pregnancy time interval after a RYGB increases the risk of iron deficiency anaemia but not of other nutritional deficits. Time interval does not seem to have an adverse effect on the obstetrical outcome, including intrauterine growth restriction. Specific attention is needed on iron deficit with increasing surgery-to-pregnancy time interval.

Keywords Pregnancy · Pregnancy complications · Roux-en-Y gastric bypass · Time interval · Vitamin deficiency · Anaemia

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Abbreviations

BMI	Body mass index
CS	Caesarean section
GDM	Gestational diabetes mellitus
HbA1c	Haemoglobin A1c
LGA	Large for gestational age
PE	Preeclampsia
PIH	Pregnancy-induced hypertension
RYGB	Roux-en-Y gastric bypass
SGA	Small for gestational age
GA	Gestational age
IFCC	International Federation of Clinical Chemistry

Introduction

The prevalence of obesity has increased dramatically worldwide over the past decades, and in 2014, 39 % of adults above age 18 were overweight (body mass index (BMI) ≥25 kg/m^2) and 13 % were obese (BMI >30 kg/m^2) [1]. This has been followed by an increased number of bariatric operations, which are considered the most effective treatment of morbid obesity, after attempted lifestyle changes have failed [2]. Three-fourth of the Danish patients having bariatric surgery in 2007–2014 were women, and half of them were in their reproductive age (age 20–40) [3].

Prepregnancy obesity is a significant risk factor for maternal and obstetrical complications [4, 5]. Weight loss after bariatric surgery improves not only fertility, but also reduces the risk of obstetrical and neonatal complications [6–8]. However, bariatric surgery may have adverse maternal and foetal effects, due to nutritional deficiencies and anatomical changes in the gut [9, 10]. Restrictive and malabsorptive procedures for treatment of severe obesity, such as the Roux-en-Y Gastric Pass (RYGB), leave the patient with a lifelong need of supplements with vitamin B_{12}, calcium and iron [2, 11]. During pregnancy, the requirements for most nutrients are increased, and nutritional deficiencies, which can be even more pronounced after gastric bypass, may have crucial influence on foetal growth and development [12–14].

Haematological and nutritional parameters may decline during the first 18 months after restrictive surgery [11]. Due to the possible malnutrition during the catabolic phase after gastric bypass and the increased nutritional demands during pregnancy, it is advised to await pregnancy until 12–18 months after surgery [15]. The aim of this study was to evaluate the impact of the time interval between RYGB and pregnancy on haematological and nutritional parameters and the obstetric outcome.

Subjects and Methods

The study group comprised women with a history of RYGB referred to Copenhagen University Hospital Hvidovre and Herlev, Denmark, for antenatal care between 2009 and 2015. Two thirds of the cohort gave birth after 1 January 2013. The women's last singleton pregnancy after the RYGB of at least 24 weeks of gestation was included in the study. Data were retrospectively collected from local medical records.

Background data included prepregnancy age, parity, weight, height, metabolic diseases and weight before RYGB. Only one woman had hypertension before pregnancy and none had pregestational diabetes. After RYGB, patients in Denmark are advised to have supplementation of iron, B-12, D-vitamin and multivitamin. Data on compliance of prepregnancy supplementation and of haematogical and nutritional status before pregnancy were not available. Obstetrical data included hypertensive disorders during pregnancy, gestational weight gain, gestational length, mode of delivery, birth weight and length, maternal haematological and nutritional status.

In Denmark, screening for gestational diabetes mellitus (GDM) is only performed when at least one of the following risk factors are present: BMI ≥27 kg/m^2, diabetes in first and second degree relatives, glycosuria, twin pregnancy, previous GDM or previous macrosomia (birth weight ≥4500 g). In women with RYGB, screening for GDM is performed by a glucose profile due to the risk of dumping at an oral glucose tolerance test. A glucose profile testing was performed by measuring capillary blood glucose just before and one and a half hour after the three main meals. The cut-off values for diagnosing GDM by a glucose profile were based on local guidelines. The cut-off was 7 mmol/L at the Hvidovre Centre and 6 mmol/L at the Herlev Centre. At the Hvidovre Centre, the patients are trained to measure the blood glucose by themselves, and the testing is performed at home. At the Herlev Centre, the women stay in hospital, and the testing is performed by a nurse. The expected date of delivery was set by ultrasound at a nuchal translucency scan in gestational week 11–13. The woman's age at pregnancy was calculated as the age at expected date of delivery minus 266 days (38 weeks). Hypertension was defined as a blood pressure ≥140/90 mmHg, preterm delivery as birth before 37 completed gestational weeks, and small for gestational age (SGA) as birth weight less than 15 % deviation from the population mean, equal to 10th centile [16, 17].

In Denmark, pregnant women are recommended daily supplementation with multivitamin, folic acid and from gestational week 10 onwards, iron (40–50 mg) [18]. Women with RYGB are also recommended supplementation with vitamin B_{12}, vitamin D and calcium [19]. Haematological and nutritional status were not routinely evaluated until 2011 where a national guideline on pregnancy in women with gastric bypass was published. For the majority of the women, the evaluation was not done until gestational week 20, when they visited the hospital for a routine malformation scan. From 2012, women with gastric bypass had regular blood tests every 4th–6th week during the second and third trimester of pregnancy, for evaluation of the haematological and nutritional status. Vitamin supplementation was increased if deficiencies were found. Information on vitamin supplementation was available for 75 % of the total cohort. Less than 1 % did not take iron, 2.0 % no multivitamins, 6.1 % no vitamin B_{12} and 3.5 % no vitamin D supplementation. Non-compliance did not differ between the women with more or less than 18 months between RYGB and pregnancy.

In the second and third trimester of pregnancy, the haematological and nutritional parameters become affected due to physiological changes related to pregnancy. Because of this, we calculated a mean value for all the measurements for each woman from gestational week 12 until delivery. The number of measurements ranged from zero to six. The concentrations were defined as low if below the following levels: Vitamin B_{12} <200 pmol/L, haemoglobin <6.5 mmol/L (10.5 g/L), ferritin <12 μg/L, vitamin D <50 nmol/L and zinc <7 μmol/L. The cut-off levels for vitamin B_{12}, vitamin D and ferritin were based on a regional laboratory manual (http://labvejl.rh.dk/LabVejl.asp). Haemoglobin levels were based on the UK guideline on anaemia in pregnancy and are specific for second and third trimester [20]. The level for zinc was based on personal experience, as we could not find reference intervals for pregnant women.

The women were stratified into two groups according to the time interval between the RYGB and pregnancy: less than 18 months (early group) and 18 months or more (late group). The women in the late group were additionally stratified into two subgroups in a sub analysis: one with onset of pregnancy between 18 months and 4 years after RYGB and one with more than 4 years between RYGB and pregnancy.

Frequencies were compared by the chi-square test and medians with the Kruskal–Wallis test. A p value of less than 0.05 was considered significant. Univariate analysis of variance was applied to explore relationships between levels of haematological and nutritional parameters and time between RYGB and pregnancy. Binary logistic regression analysis was used to adjust for covariates. Statistical analyses were performed using SPSS version 22.

Results

In the study population of 153 women, 40 women had an early pregnancy (<18 months between RYGB and pregnancy) and 113 a late pregnancy (≥18 months after RYGB). The early and late groups of women were comparable according to preRYGB BMI, prepregnancy BMI, parity and age (Table 1).

Iron deficiency, anaemia and iron deficiency anaemia occurred with a significantly higher frequency in the late group (Table 2). Although haemoglobin A1c (HbA1c) was significantly higher in the late versus early cohort ($p = 0.027$), there was no difference in frequency of high HbA1c (≥38 mmol/mol).

Of the 113 women in the late group, 27 women delivered more than 4 years after the RYGB. Compared to women in the early group (delivery less than 18 months after RYGB), women with a delivery more than 4 years after the RYGB had a significantly higher risk of ferritin deficiency (17/24 (70.8 %) vs. 14/37 (37.8 %), $p = 0.012$). They also had a trend towards a lower median ferritin concentration of (9.6 vs. 14.8 μg/L, $p = 0.094$). There was no significant difference in median haemoglobin concentration (6.7 vs. 7.1 mmol/L, $p = 0.213$), but significantly more women with more than 4 years between gastric bypass, and pregnancy had a haemoglobin below 6.5 mmol/L (10/26 (38.5 %) vs. 5/38 (8.6 %), $p = 0.019$). No significant difference was found for the concentration of vitamin B_{12}, vitamin D and zinc in the subgroup analysis (data not shown).

There was no significant difference in the risk of preterm delivery, pregnancy-induced hypertension (PIH), preeclampsia (PE), mode of delivery, birth weight, SGA or large for gestational age (LGA) (Table 3). The median birth weight was almost 200 g lower in the early group compared to the late group, but this was not statistical significant. There was no association between iron deficiency anaemia and low birth weight (SGA) (data not shown). None of the women developed GDM.

The rate of caesarean section (CS) was high in both groups: 42.5 % in early cohort and 38.1 % in the late cohort. Half of the elective CSs was on maternal request. Five women in the early group and two in the late group had a caesarean section due to upper abdominal pain and suspicion of internal herniation. The CS was elective in three of the five in the early group and in one of the two in the late group.

Discussion

In this study, we found that an interval of more than 18 months between gastric bypass and pregnancy was associated with lower ferritin and haemoglobin, resulting in iron deficiency, anaemia and iron deficiency anaemia. No other disruption in nutrient status (vitamin B_{12}, vitamin D and zinc) was found. The antidiabetic effect of the gastric bypass seams to decrease over time as indicated by an increasing HbA1c the longer the time interval from gastric bypass to pregnancy. However, none developed GDM although pregestational BMI was still high. We found no relationship between a short surgery-to-pregnancy time interval and low birth weight or growth restriction.

Table 1 Baseline characteristics in women stratified according to time from Roux-en-Y gastric bypass to pregnancy

Time interval	<18 months	≥18 months	[*N*]	*p*
Number of women	40	113		
Delivery before year 2012	6 (15.0)	5 (4.4)	40/113	0.026
Time from RYGB to pregnancy (months)	13.7 (1.8–18.0)	37.3 (18.5–83.4)	40/113	<0.0005
Prepregnancy age (years)	31.9 (25.0–43.6)	31.8 (22.1–41.2)	40/113	0.889
BMI before RYGB (kg/m^2)	43.7 (35.3–55.4)	44.7 (34.2–75.2)	35/100	0.055
BMI prepregnancy (kg/m^2)	27.5 (21.4–40.8)	29.0 (21.0–46.3)	40/113	0.094
Primiparity (%)	19 (47.5)	50 (44.6)	40/112	0.755

Data are expressed as median (range) or number (%). [*N*] number with available data for pregnancy </≥ 18 months after RYGB

RYGB Roux-en-Y gastric bypass, *BMI* body mass index

Table 2 Haematological and nutritional levels and the frequency of deficiency in pregnancies according to time since Roux-en-Y gastric bypass

Time interval	<18 months	≥18 months	[*N*]	*p*
Number of women	40	113		
Vitamin B_{12} (pmol/L)	337 (144–868)	319 (119–1481)	37/103	0.487
vitamin B_{12} <200 pmol/L	3 (8.1)	12 (11.7)		0.550
Ferritin (μg/L)	15 (4–210)	10 (2–160)	37/103	0.079
Ferritin <12 μg/L	14 (37.8)	63 (61.2)		0.014
Haemoglobin (mmol/L[a])	7.1 (6.3–7.8)	6.9 (4.8–8.9)	38/109	0.244
Anaemia (Hgb <6.5 mmol/L)	5 (13.2)	36 (33.0)		0.019
Iron deficiency anaemia[b]	3 (8.1)	30 (29.1)	37/103	0.010
Zinc (μmol/L)	8 (6–13)	8 (6–13)	34/102	0.226
Zinc <7 μmol/L	3 (8.8)	11 (10.8)		0.745
25-OH-vitamin D2 + D3 (nmol/L)	65 (19–145)	66 (17–132)	37/103	0.737
vitamin D <50 nmol/L	8 (21.6)	26 (25.2)		0.660
HbA1c (IFCC, mmol/mol)	31 (25–38)	33 (24–41)	33/92	0.020[c]
HbA1c ≥38 mmol/mol	1 (3.0)	11 (12.0)		0.135

Data are expressed as median (range) or *n* (%). [*N*] number with available data for pregnancy </≥ 18 months after RYGB

Hgb haemoglobin, *RYGB* Roux-en-Y gastric bypass, *HbA1c* glycated haemoglobin, *IFCC* International Federation of Clinical Chemistry units

[a] Conversion from millimole per liter to grams per deciliter: Hgb in mmol/L × 1.1611

[b] Ferritin <12 μg/L and haemoglobin <6.5 mmol/L

[c] Correlated for weight difference from RYGB to pregnancy

Low haemoglobin in women with more than 4 years' interval between gastric bypass and pregnancy, as found in our study, has also been found by Nomura et al. [21]. Iron deficiency anaemia is the most common form of anaemia and the most prevalent deficiency disorder in pregnancy [22]. After RYGB, it is common to experience intolerance to certain foods, especially red meat, resulting in very low iron intake. In addition, the bioavailability of iron is decreased after RYGB due to less gastric acid and bypass of the duodenum [21]. Furthermore, iron stores decline over time after RYGB,

Table 3 Obstetrical outcome according to time interval between Roux-en-Y gastric bypass and pregnancy

Time interval	<18 months	≥18 months	[*N*]	*p*
Number of women	40	113		
PIH or PE	2 (5.4)	13 (12.7)	37/102	0.218
Gestational weight gain (kg)	9.4 (−2.0–21.6)	10.1 (−0.3–35.1)	30/90	0.316
Induced labour	10[a] (32.6)	31[a] (35.2)	31/88[a]	0.765
Caesarean section	17 (42.5)	43 (38.1)	40/113	0.621
Elective CS	9 (52.9)	24 (55.8)	17/43	0.840
Maternal request CS	6 (66.7)	9 (41.7)	17/43	0.201
Preterm delivery	7 (17.5)	14 (12.4)	40/113	0.420
Birth weight (gram)	3064 (2056–4178)	3258 (1025–4500)	39/112	0.071
Gestational age (days)	272 (226–292)	272 (219–294)	40/113	0.627
Small for GA	9 (23.1)	17 (15.2)	39/112	0.261
Birth weight ≥4000 g	2 (5.1)	11 (9.8)	39/112	0.368
Birth weight ≤2500 g	4 (10.3)	12 (10.7)	39/112	0.936
Large for GA	1 (2.6)	1 (0.9)	39/112	0.432

Data are expressed as median (range) or *n* (%). [*N*] number with available data for pregnancy </≥ 18 months after RYGB

RYGB Roux-en-Y gastric bypass, *PIH* pregnancy-induced hypertension, *PE* preeclampsia, *CS* caesarean section, *GA* gestational age

[a] Excluding Elective Caesarean section

and these patients are at high risk of developing iron deficiency anaemia [23]. It has been suggested that the compliance to taking supplements after RYGB decline over time, which may explain the higher incidence of low ferritin in the group with more than 18 months' interval [21]. According to Ribot et al., iron deficiency before or early in pregnancy may lead to low birth weight even if patients are not yet anaemic [24]. Maternal anaemia due to iron deficiency at the beginning of the pregnancy has previously been associated with preterm delivery and low birth weight [25] and is more frequent in women with more than a 4-year postoperative interval [21]. We did not have enough data on pre- and early pregnancy haematological and nutritional status to explore this association. However, based on our result with increasing incidence of iron deficiency, the longer the time between RYGB and pregnancy, one would expect an increasing risk of preterm labour and low birth weight. However, this was not found in our study. Furthermore, the compliance for especially oral iron supplementation seemed high in the present cohort. The other evaluated nutrients (vitamin B_{12}, vitamin D and zinc) do not seem to complicate pregnancies after gastric bypass in case of regular vitamin supplementation.

Women in the fertile age having RYGB are often advised to await pregnancy until 12–18 months after surgery, as the first year is the time of most rapid weight loss. During this catabolic phase the nutritional intake declines while the requirements for nutritional intake increases due to the growing foetus. Hence, there is a risk for adverse effects on foetal growth. However, the literature does not indicate a difference in perinatal outcome or pregnancy complications in women becoming pregnant within the first year or later after bariatric surgery [8, 15, 26]. This supports the finding in our study with no relationship between a short surgery-to-pregnancy time and low birth weight or growth restriction. These and previous similar findings can be explained by a close monitoring with frequent evaluation of nutritional status and supplementation accordingly [15, 26, 27]. In addition, the compliance might be higher closer to the time of surgery due to awareness. Although there is no documentation of adverse effect on the foetus by obtaining pregnancy soon after RYGB, apart from lower birth weight and shorter gestational duration, there might be not yet documented side effects [25]. To our knowledge, there are no data on long-term follow-up regarding psychological and physical performance in children born by women, who became pregnant during the catabolic phase after RYGB.

Bariatric surgery has a positive effect on glucose metabolism with reductions in fasting glucose levels and in HbA1c [2]. Our study showed that none of the women developed GDM during pregnancy, but median haemoglobin A1c was significantly higher in the late group than in the early. It is well known that the initial weight loss after bariatric surgery is often followed by some weight gain and thereby an increased risk of insulin resistance. The higher HbA1c in the late group found in our study may indicate that the positive effect of bariatric surgery on blood glucose levels and insulin sensitivity diminishes over time. The rate of caesarean section was high in both groups with a two-time higher frequency than the average rate in Denmark of approximately 21 % [28]. The proportion of women with an elective caesarean section upon maternal request could not explain these high rates. Sheiner et al. have suggested that bariatric surgery is an independent risk factor for caesarean section, even after controlling for confounders such as obesity, previous caesarean section and labour induction [29]. However, they did imply that it might be a result of caregiver bias.

Limitations of the study are the number of included women, which results in a difficulty in detecting small but clinical relevant differences, and the lack of data on prepregnancy supplementation and nutritional status. In addition, data on haematological and nutritional parameters were not available for all the women, and regular haematological and nutritional screening were first introduced 3 years into the study period. Yet, the majority (three-fourths) of the cohort gave birth after the publication of a national guideline for handling pregnant women with gastric bypass. The strength of our study is that we collected data from medical records, so recall bias was avoided. Also the cohort size exceeds the majority of cohort studies in women with gastric bypass.

Conclusion

The present study has shown that the longer the time between RYGB and pregnancy, the more depleted are the iron stores, resulting in iron deficiency anaemia even with relevant iron supplementation. No other nutritional deficiency was found. The pregnancy outcome was similar in women obtaining pregnancy within the first 18 months after RYGB and later. The fear of increased risk for pregnancy complications during the 18 months may be exaggerated. Yet, we do not know the long-term effect on the outcome, which calls for precautions against pregnancy during the catabolic phase. When following international recommendations for nutritional supplementation in pregnancy after RYGB, the clinician can focus on haemoglobin and iron status. Focused care can have an important impact on compliance.

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Compliance with Ethical Standards

Ethical Approval The Danish board of Data Protection approved the study (Journal Number 2012-41-1006).

Conflict of Interest The authors declare that they have no conflict of interest.

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